Adrenocorticotropic and Cortisol Levels in the Plasma of Bovine Fetuses and Neonates

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ABSTRACT. Plasma ACTH and cortisol levels in the bovine fetuses over the period of 5 to 9 months of gestation and in the neonates immediately after birth and at 5 days old were studied. In the bovine fetuses, the plasma ACTH levels ranged from 60.8±17.8 to 71.3±19.7 pg/ml over the period of 5 to 7 months of gestation. It increased rapidly to 239.2±261.5 pg/ml at 8 months and to 406.9±409.4 pg/ml at 9 months of gestation. In the neonates immediately after birth it decreased to 182.3±110.7 pg/ml. The plasma cortisol levels ranged from 3.23±2.12 to 3.85±2.52 ng/ml over the period of 5 to 8 months of gestation and increased to 8.10±4.88 ng/ml at 9 months of gestation. It then increased rapidly to 88.35±42.78 ng/ml in the neonates immediately after birth. The correlation between plasma ACTH and cortisol levels in the fetuses of 5 to 7 months of gestation was not significant, but in the fetuses of 8 and 9 months of gestation and neonates were significant. However, especially immediately after birth, the increase in plasma cortisol occurred without a concomitant rise in plasma ACTH. According to these findings, it is suggested that the pituitary-adrenocortical axis in bovine fetus matures in the later stage of gestation and an increase of sensitivity in the fetal adrenal gland to ACTH may serve as a trigger for the onset of parturition.---KEY WORDS: ACTH, cortisol, bovine fetus, neonate.

Liggins et al. [12] observed that the hyperfunction of the adrenal cortex in the ovine fetus immediately before birth served as a trigger for the onset of parturition for pregnant ewes. They suggested that the anterior pituitary might participate in the mechanism which caused this hyperfunction and that ACTH might be a factor regulating this mechanism. It has been reported that corticoid and ACTH increased gradually in concentration toward the onset of parturition in sheep [8, 10] and rose rapidly with ACTH in pigs [6], goats [11] and sheep [20]. However, a prepartum increase in fetal plasma cortisol occurred without a concomitant rise in ovine fetal plasma ACTH [19]. Hitherto, there are limited reports on the pituitary-adrenal function in the bovine fetus. The present studies were carried out to clarify the relationship between plasma ACTH and cortisol in the bovine fetus and neonate.

MATERIALS AND METHODS

Live bovine fetuses were collected from the uteri of 31 pregnant dairy cows of hybrid Holstein breed immediately after sacrificing the cow. The fetal length was measured by the crown-rump length method and the fetal age was estimated by the method described in the previous report [21]. Fetal blood was collected in a vacuum tube contained EDTA-2Na by the direct cardiac puncture from the chest wall. The plasma was then separated and stored in a frozen state. Samples were collected between 09:00 and 11:00 h.

Neonates delivered normally from 8 hybrid Holstein cattle were employed to collect the blood from the jugular vein immediately after birth and on the 5th day of
age at the time between 09:00 and 11:00 h. The plasma was separated and stored in a frozen state.

The plasma ACTH was determined by using a ACTH radioimmunoassay kit from Amersham International Plc (Amersham, Bucks, UK). The ACTH antibody had high specificity against the amino acid (1–24)-ACTH. The sensitivity was considered to be 25 pg/tube. The intra- and inter-assay coefficients of variation were less than 11% and 16%, respectively.

Cortisol was determined in the plasma by radioimmunoassay using the procedure described by Makino [14]. The antiserum against cortisol-21-hemisuccinate-BSA was purchased from Tikoku Hormone Mfg. Co. (Tokyo, Japan). Cross-reactivity with steroids such as cortisone, aldosterone and corticosterone were 28.1%, 2.9% and 2.9%, respectively. The sensitivity of the assay was 10% pg/tube; intra- and inter-assay coefficients of variation were less than 8% and 12%, respectively.

Age-related differences in plasma ACTH and cortisol levels were statistically analysed by student's t test. Relationships between ACTH and cortisol levels in the fetuses and neonates were indicated by correlation coefficient and regression coefficient. The significance was analysed by variance analysis.

RESULTS

The plasma ACTH levels in the bovine fetuses are plotted in Fig. 1-A. They ranged between 60.8±17.8 (mean±SD) and 71.3±19.7 pg/ml over the period of 5 to 7 months of gestation. They increased markedly to 239.2±261.5 and 406.9±409.4 pg/ml at 8 and 9 months of gestation, respectively. There was a significant difference (p<0.01) between the levels of 5 to 7 months and 8 and 9 months of gestation. The plasma ACTH levels in the neonates immediately after birth and at 5 days old were 182.3±110.7 and 99.9±53.6 pg/ml, respectively. No significant difference was found between the ACTH levels of 8 and 9 months of gestation and neonates, but a trend of gradual decrease was clearly found. The plasma cortisol levels in the fetuses are plotted in Fig. 1-B. They ranged between 3.23±2.12 and 3.85±2.52 ng/ml over the period of 5 to 8 months of gestation and increased rapidly to 8.10±4.88 ng/ml at 9 months of gestation. The levels increased rapidly to 88.35±42.78 ng/ml immediately after birth. There was a significant difference (p<0.001) between the cortisol levels of fetuses and neonates immediately after
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Fig. 2. Correlations between plasma cortisol and ACTH levels in the bovine fetuses and neonates. Plots indicate the correlation between the ACTH and cortisol levels in the fetuses over the period of 5 to 7 months of gestation [plot I (●); r = −0.186, p > 0.05 and n = 17], in the fetuses at 8 and 9 months of gestation [plot II (○); r = 0.540, p < 0.05 and n = 14] and in the neonates immediately after birth and at 5 days old [plot III (▲); r = 0.764, p < 0.01 and n = 16].

The levels then decreased to 14.09±5.83 ng/ml at 5 days old.

The correlations (plots I, II, III) between plasma ACTH and cortisol levels in the fetuses and neonates are shown in Fig. 2. The correlation between the ACTH and cortisol levels in the fetuses over the period of 5 to 7 months of gestation (plot I) was not significant (r = −0.186, p > 0.05 and n = 17), but in the fetuses at 8 and 9 months of gestation (plot II) there was a significance (r = 0.540, p < 0.05 and n = 14). The latter regression coefficient was 0.012, indicating the ACTH levels were much higher than any given correlated cortisol levels. The correlation between plasma ACTH and cortisol levels in the neonates immediately after birth and at 5 days old (plot III) was also proved to be significant (r = 0.764, p < 0.01 and n = 16). The regression coefficient was 0.383, indicating the cortisol levels were much higher than any given correlated ACTH levels. However, this correlation was markedly significant immediately after birth and the increase in plasma cortisol occurred without a concomitant rise in plasma ACTH. The regression coefficient between the fetuses at 8 and 9 months of gestation (II) and neonates (III) showed a significant difference (p < 0.01).

DISCUSSION

It is well accepted that the fetal pituitary-adrenal axis plays an important role in the physiological process that initiates its own delivery. The cortisol rise in ovine fetus started from 6 to 9 days [3, 20] or around 20 days [7, 13] before parturition. Histological studies on the fetal adrenal support the latter, since the number of mature cells in the zona fasciculata increases after 120 days of gestation in ovine fetus [17, 22]. Hennesy et al. [7] suggested that the majority of the cortisol in the blood of ovine fetuses during 100–121 days of gestation originates from maternal rather than fetal sources. However, it accounted for only 37% of the cortisol measured in fetuses of 122–135 days and 12% or less in fetuses older than 136 days of gestation. In the guinea-pig, most of the cortisol in fetal plasma is from maternal origin until the end of pregnancy [4].

In this study, the plasma cortisol levels in bovine fetuses were found to be low over the period of 5 to 8 months of gestation and to increase gradually at 9 months of gestation. Immediately after birth, the cortisol level rapidly increased. The fetal plasma cortisol level over the period of 5 to 8 months of gestation was lower than that of the pregnant cow [9], except during the period near term, and it was suggested that during the period of 5 to 8 months of gestation there was a little cortisol release from the bovine fetal adrenal gland. In the
obvine fetus, cortisol secretion from the fetal adrenal gland seemed to be activated at 9 months of gestation.

Winters et al. [23] mentioned that the concentration of ACTH in cord plasma prior to the 34 week of gestation was 241±33 pg/ml, and in term fetuses, the ACTH level was 143±7 pg/ml in the human. They suggested that an increased output of corticosteroids from the growing adrenal may have depressed ACTH secretion in the human. Basal levels of plasma ACTH in ovine fetus increase concomitantly with cortisol at 140 days or more in half of the fetuses [10] or after 122 days, and particularly 2 days before parturition [8, 16]. The ACTH level peaks at term in sheep [20] and at 1 day before delivery in goats [11]. Moreover, in sheep [1], rat [15] and humans [2, 23] ACTH of the hypophysis is seldom or never transferred from mother to fetus.

In the present study, the plasma ACTH level was low over the period of 5 to 7 months of fetal age, but increased significantly (p<0.01) at 8 and 9 months of gestation. There was no significant correlation between plasma ACTH and cortisol levels in the bovine fetuses over the period of 5 to 7 months, but a significant positive correlation between the fetuses of 8 and 9 months of gestation and neonates immediately after birth and at 5 days old.

In ovine fetuses, between 90–120 days of gestation, exogenous ACTH is relatively ineffective in stimulating cortisol [24], and there is no correlation between endogenous plasma ACTH and cortisol levels [8, 10]. In the ovine fetuses, which are older than 121 days of gestation, the adrenal becomes increasingly responsive to exogenous ACTH [12, 25]. Further, there is a significant correlation between endogenous ACTH and cortisol values [8].

In this study, the fetal plasma ACTH and cortisol levels showed a increase before birth. However, careful examination of the changes in both hormonal levels showed that the distinct rise in fetal plasma cortisol did not coincide with the fluctuation of fetal plasma ACTH level, immediately after birth. The ACTH levels at that time were lower than that of 8 or 9 months of gestation. Likewise, Kuwabara [11] also pointed out that in the fetuses of goat the blood cortisol level started to increase suddenly 4 days before birth. However, this increase was not always in parallel with the ACTH level. Rose et al. [18, 19] also mentioned that a prepartum increase in ovine fetal plasma cortisol occurred without a concomitant rise in plasma ACTH. These changes seem to show an increase in adrenal sensitivity to ACTH as term approaches. At term, the number of ACTH receptors in membrane or cell preparation from ovine adrenal glands increases 5-fold between day 123 of gestation and birth [5].

Accordingly, it is conceivable that a hypothalamic-pituitary-adrenocortical axis in the bovine fetus matures just before birth and an increase in sensitivity of fetal adrenal gland to ACTH serves as a trigger for parturition.

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要約

牛胎子と新生児における血中副腎皮質刺激ホルモンとコルチゾール値の推移：武石昌敬・柴田 真・津曲茂久（日本大学農獸医学部獣医臨床繁殖学研究室）—牛胎子の妊娠5～9ヶ月および新生児の出生直後と5日目の血中ACTHとコルチゾール値について検討した。その結果、牛胎子血中ACTHは妊娠5～7ヶ月で60.8±17.8 pg/mlから71.3±19.7 pg/mlの範囲で推移したが、8ヶ月で239.2±261.5 pg/ml、9ヶ月では406.9±409.4 pg/ml上昇した。出生直後の新生児では、182.3±110.7 pg/mlに低下した。牛胎子血中コルチゾール値は妊娠5～8ヶ月で3.23±2.12 ng/mlから3.85±2.52 ng/mlの範囲で推移したが、9ヶ月でやや上昇し、新生児の出生直後で88.35±42.78 ng/mlと急増した。胎子期の5～7ヶ月におけるACTHとコルチゾール値との間には相関性は見られなかったが、8～9ヶ月および新生児においては有意な正の相関が見られた。しかし、出生直後の血中コルチゾール値が急増したのに対しACTH値の同期的増加は見られなかった。このことより牛胎子の下垂体－副腎皮質系は妊娠末期に成熟し、胎子副腎のACTHに対する感受性の増加が分娩誘発の引金となることが示唆された。